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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/767,215	01/22/2001	John Bertin	07334-142001/ MPI2000-003	3061

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/767,215	BERTIN, JOHN	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,21,25-32,34 and 37-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,2 and 32* is/are allowed.

6)☒ Claim(s) *21,25-31,34 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07/01/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 3-20, 22-24, 33, 35-36.

Accordingly, claims 1-2, 21, 25-32, 34, 37-40 are being examined.

Claims 1-2, 32 are free of prior art and are allowable.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph of claims 21, 25-31, 34, 37-40 remain, because the specification, while being enabled for the amino acid sequence of SEQ ID NO:2, is **not enabled for a polypeptide "comprising" amino acids 10-116, or 826-1004 of SEQ ID NO:2, or a polypeptide that is at least 85%, 95% , or 98% identical to SEQ ID NO:2, wherein said polypeptide binds to Bcl-10 or activates NF-kB**, remains for reasons already of record in paper No.17 of 08/26/03.

Applicant argues as follows:

1) How to make and use polypeptides containing the caspase recruitment domain (CARD) or Guanylate Kinase (GUK) domain of CARD-14.

Applicant argues that a CARD domain is a protein-binding module that mediates the assembly of CARD-containing proteins into apoptosis and NF-KB signaling complexes, and that a GUK domain is a GTP-binding domain that, together with a PDZ

and an SH3 domain, is found in members of the membrane-associated guanylate kinase (MAGUK) protein family, to which CARD-14 belongs.

Applicant argues that because Claims 21 and 25 require, respectively, that the claimed polypeptide contain the amino acid residues that correspond to the intact functional CARD (claim 21) or GUK domain (claim 25) of CARD-14, the polypeptides necessarily retain the functional activity of the respective domain.

Applicant argues that the CARD (about amino acids 10-116 of SEQ ID NO:2) of CARD-l4 binds to the CARD of Bcl-10. Applicant argues that accordingly, a polypeptide containing amino acids 10-116 of SEQ ID N0:2 *necessarily* binds to Bc1-10. The CARD-containing polypeptide of claim 21 can therefore be used to screen for compounds that modulate the CARD-14-Bc1-10 interaction, and thereby blocking cell signaling processes that results from the interaction.

Applicant argues that the GUK domain of CARD-14 is expected to be a GTP-binding domai, and this is expected to *necessarily* bind to GTP. Applicant argues that the GUK-containing polypeptide of claim 25 can therefore be used to screen for compounds that modulate the CARD-14-mediated signal transduction and therefore, modulates, for example, CARD-14 mediated apoptosis and/or inflammation.

Applicant's arguments set forth in paper of 01/30/04 have been considered but are not deemed to be persuasive for the following reasons:

The claims 21, 25 encompass sequences of any length with unknown structure and function, that are attached to the CARD domain of SEQ ID NO:2, or to the GUK domain of SEQ ID NO:2, wherein the effect of these sequences on: 1) the binding of the

CARD domain of SEQ ID NO:2 to Bcl-10, or of the GUK domain of SEQ ID NO:2 to GTP, such as steric hindrance, 2) mediating of the CARD interactions between the claimed sequences and the target proteins, such as bcl-10 or a caspase, and 3) the actual CARD interactions between the claimed sequences and the target proteins, such as bcl-10 or a caspase, which are not necessarily structurally related to the claimed sequences, is unpredictable.

There is no teaching which structure of the numerous sequences, that are attached to the CARD domain of SEQ ID NO:2, or to the GUK domain of SEQ ID NO:2, allow non-steric hindrance for their binding. It is well known in the art however that a specific binding of a ligand to a substrate requires specific interaction between the ligand and the substrate, and correct conformation of the ligand to fit into the binding site of the substrate. Thus one cannot predict that the claimed sequences would have the necessary conformation for specifically binding to Bcl-10 or GTP.

Further, it is well known in the art that a CARD-containing polypeptide activates a caspase by forming a hetero-oligomer with the caspase and in this complex, the CARD-containing polypeptide allosterically upregulates the caspase activity (Shiozaki E N, 2002, Proceed Natl Acad Sci, USA, 99 (7): 4197-202). It is also well known in the art that oligomerization of a caspase is induced by the CARD-containing polypeptide, and is required for casapse activation (Lee S H et al, 2001, J Biol Chem, 276(37): 34495-500). The specification however has not shown that the claimed polypeptides would have structure necessary for forming a hetero-oligomer with Bcl-10 or caspase, to

induce the oligomerization of caspases upon interaction with caspases via the CARD domain.

Similar reasons for rejection apply for the claimed sequences that activate NF-kB or stimulate Bcl-10 phopsphorylation.

Moreover, even if the claimed sequences could bind to Bcl-10 or GTP, one does not know how to use the claimed polypeptides for useful purpose. Although the claimed sequences could be used for screening agents that inhibit the CARD-14-Bcl-10 interaction, or the CARD-14-GTP interaction, one cannot predict that the screened agents would have any use, such as mediating apoptosis or inflammation, in view that one cannot predict that CARD-14 is responsible for apoptosis or inflammation. Although SEQ ID NO:2 has a CARD-like domain, and could bind to Bcl-10 via said domain, and activates NF-kB, one cannot predict that CARD-14 is responsible for apoptosis or inflammation because CARD domains could have function other than in apoptosis, and because activation of NF-kB does not necessarily lead to apoptosis. Willis et al teach that CARD domains could have function other than in apoptosis . e.g. the prodomain of caspase-2 contains a CARD that allows nuclear translocation, and that truncated Bcl10 activates NF-kB but does not induce apoptosis (Willis et al, 1999, Cell 96: 35-45, abstract and p.41, second column, paragraph before last, last four lines). Further, it is well known in the art that NF-kB is involved in many different pathways in a cell, and which pathways are affected is not predictable. Thus in view of the above, one does not know how to use the claimed polypeptide for useful purposes.

2. How to make and use polypeptide sequence variants CARD-14.

Applicant argues that it is within the grasp of one of skill in the art to prepare the claimed polypeptides, using the standard method of mutagenesis. Applicant argues that one can screen for variants that retain the specific CARD-14 functional activity.

Applicant recites Bowie et al, 200, stating that proteins are surprising tolerant of amino acid substitutions, and that about half of all substitutions are phenotypically silent, and thus the question is whether one can produce without undue experimentation mutants in which the activity is not abolishes.

The recitation of Bowie et al is acknowledged.

Applicant has not shown how to make variants of SEQ ID NO:2, such that they function as claimed. Applicant has not shown how to change 3%, 5% or 15% at any amino acid position of SEQ ID NO:2 and still result in a polypeptide that activates NF-kB or stimulates phosphorylation of Bcl-10, or a polypeptide that has the function of SEQ ID NO:2.

Contrary to Applicant assertion, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid

substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306).

The claims encompass variants having substitution, deletion or addition at any amino acid position of SEQ ID NO:2. Further, Applicant has not taught which domain(s) of SEQ ID NO:2 is responsible for stimulating Bcl-10 phosphorylation, or for activating NF-kB, or is critical for the function of SEQ ID NO:2. Protein chemistry however is unpredictable, wherein change of a single amino acid could often dramatically affect the biological activity and characteristics of a protein, as taught by Burgess et al, Lazar et al, Tao et al and Gillies et all, all of record. In view of such unpredictability, one would not know which amino acid(s) could be deleted, or substituted or added, such that the claimed polypeptide still has the function of SEQ ID NO:2, and with such unpredictability, it would be undue experimentation for one of skill in the art to screen the claimed variant sequences.

Therefore, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS
August 19, 2004

SUSAN UNGAR, PH.D
PRIMARY EXAMINER